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Review Article

A review: Immunological markers for malignant salivary gland tumors

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ABSTRACT

Salivary gland cancers are rare. Around 8 out of 10 salivary gland tumors (80%) are in the parotid. Just fewer than 2 out of 10 salivary gland cancers develop in the other two salivary glands – the submandibular or sublingual glands. Fewer than 1 in 10 cancers start in the minor salivary glands. There are many different types of salivary gland cancers. The most common is mucoepidermoid carcinoma (MEC). Just over 3 out of 10 (25–35%) salivary gland cancers (SGT, SGC) are of this type. The others include adenoid cystic carcinoma (ACC), acinic cell carcinoma, carcinoma ex-pleomorphic adenoma (Ca-PA), polymorphous low grade adenocarcinoma (PLGA) and some newly discovered salivary gland tumors. Because of the infrequency of salivary gland tumors and their complex histopathological diagnosis, it is difficult to exactly predict their clinical course by means of its recurrence, malignant progression or metastasis. Salivary gland tumors always pose problems in diagnosis.

This review provides an insight into the recent concepts and immunohistochemical markers to diagnose the malignant salivary gland tumors (SGT), thus guiding the Ear, Nose and Throat specialists, Oral and Maxillofacial Surgeons, General Pathologists and other medical and dental specialists thereby enabling them to make correct diagnosis and provide the appropriate treatment.

1. Review

1.1. *Introduction to salivary gland malignancies*

Salivary gland neoplasms are a rare group of tumors; the annual incidence rate is 1 in 100,000, comprising about 3% of all head and neck neoplasms. These tumors are rare, with an overall incidence of approximately 2.5 cases–3 cases per 100,000 per year in the Western world. Salivary gland tumors account for about 5% of all neoplasms of the head and neck.[1]

Cancer of the salivary gland usually develops in the largest of the salivary glands – the parotid glands around 75% of which only about 20% are malignant, 15% are located in minor salivary glands of the upper digestive tract. 10% arise in the submandibular glands, and less than 1% presents in the sublingual glands.

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2. Etiology

The etiology of SGTs is so far unknown. Putative risk factors include cigarette smoking, viral infections, rubber manufacturing workers, genes etc. The only well-established risk factor is ionizing radiation. Atomic bomb survivors and patients undergoing radiation therapy have a substantially higher risk of developing SGTs.[2]

Most patients with malignant tumors of the major or minor salivary glands present with painless swelling, paresthesia or anesthesia.

3. Normal histology of acini of salivary gland

Salivary gland tumors represent the most heterogeneous group of tumors of any tissue in the body. Although almost 40 histological types of SGTs exist, some are exceedingly rare. The entire glandular structure of the salivary gland is said to exhibit a two-tiered organization comprising luminal cells (acinar and ductal cells) and abluminal cells (myoepithelial and basal cells).[1]

The luminal cell from normal salivary glands has the following antigen profile:

- the acinar cells are intensely positive to cytokeratins with low molecular weight, weak positive for cytokeratins with high molecular weight, intense positive to Amylase, weakly positive for Lactoferrin, Lysosyme, Carcinoembryonic Antigen (CEA), negative to Epithelial Membrane Antigen (EMA), Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of intercalated ducts is intensely positive to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, intense positive to EMA, Lactoferrin, Lysosyme, weakly positive for CEA and SC, and negative for Amylase, Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of striated ducts shows intense positivity to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, moderately positive for S-100, weak positive to SC and negative for Lactoferrin, Lysosyme, CEA, EMA, Amylase, Vimentin, Actin, Myosin, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of excretory ducts is intensely positive to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, moderate positivity for EMA, weakly positive to SC and negative to Lactoferrin, Lysosyme, CEA, Amylase, Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase.[3,4]

Although hematoxylin-eosin staining is still the gold standard method used for diagnosis, immunohistochemistry (IHC) can enhance the accuracy of the diagnosis.[5] They can help in differentiating between luminal and abluminal cells (Table 1) and can help in understanding the complex architecture of SGTs and aid in diagnosis.[1,3]

All four cells are usually pan-cytokeratin (CK) [AE1/AE3]-positive; and S-100 protein staining is variable. Both ductal and acinar cells are epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA)-positive, while only acinar cells are α-amylase-positive. Myoepithelial and basal cells are CK14 and p63-positive and are EMA and CEA-negative; the expression of α-smooth muscle actin (SMA), muscle specific actin (MSA), calponin, podoplanin and vimentin are only observed in myoepithelial cells.[4,5]

Abluminal cells are detected for high molecular weight CK (such as E12 or CK14) and myoepithelial cells. In addition, they are stained with antibodies against myoid proteins (such as muscle specific actin, smooth muscle actin or calponin). Another myoepithelial marker is maspin, a serine protease inhibitor that functions as a tumor suppressor and is seen in tumors where both myoepithelial and basal cells are affected such as PA, basal cell adenoma, ACC and epithelial-myoepithelial carcinoma where maspin expression was high. Low proportions were seen in salivary duct carcinomas. Ductal cells are usually negative or show only weak focal immunoreactivity for maspin.[5]

CEA (whose functions include signal transduction, cooperation with proto-oncogenes in cellular transformation and inhibition of proliferation of epithelial tumors) immunoreactivity was usually detected in the cytoplasm of epithelial cells and luminal contents of neoplastic glands.[4]

Adenoid cystic carcinoma (Tables 2a and 3).

ACC occurs due to neoplastic transformation of salivary acinar-type cells and myoepithelial cells and commonly arises in parotid glands and frequently produces a mucinous or basement membrane-like extracellular matrix.

It is a slow-growing tumor with a poor prognosis in long standing cases.[6,18] The underlying cause of ACC is unknown. It is neither inherited nor associated with smoking or alcohol consumption. It may be the result of genetic alteration, a new fused gene (MYB-NFIB) created by the fusion of two broken chromosomes (numbers 6 and 9).[2,7] The most common site of metastatic spread of ACC is to lungs, liver and bone.[18]

Adenoid cystic carcinoma is characterized by a [t (6; 9) (q22-23; p23-24)] translocation of head and neck[19] and the breast.[5,6]

Table 1 – Immunohistochemical markers for malignant salivary glands.

Antigen	Luminal cells		Abluminal cells	
	Acinar	Ductal	Myoepithelial cells	Basal cells
CK[AE1/AE3] [Pan-cytokeratin][5]	+ve	+ve	+ve	+ve
EMA,CEA[5]	+ve	+ve	−ve	−ve
α-amylase-positive[5]	+ve	−ve		
CK14[6]			+ve	+ve
p 63[5]			+ve	+ve
α-smooth muscle actin (SMA),[5] Muscle specific actin (MSA)[5]				
Calponin[6]			+ve	−ve
Podoplanin[5]			+ve	−ve
Vimentin[5]			+ve	−ve
S-100[4]	Variable	Variable	Variable	Variable

These genes are associated with apoptosis, cell cycle control, cell growth/angiogenesis and cell adhesion. Deregulation of MYB and its target genes may be a key oncogenic event in the pathogenesis of ACC.[1]

Genes overexpressed in ACC include Sox 4, keratin 17, transmembrane 4 superfamily member 1 and laminin. The most under-expressed genes are those encoding for proteins of acinar-type differentiation (e.g. amylase, carbonic anhydrase and salivary proline-rich proteins). The basement membrane proteins were more highly ranked than normal salivary gland. Extracellular matrix proteins such as chondroitin sulfate were seen. Wnt/catenin pathway is not overtly dysregulated in ACC, as it is, for example, in colorectal carcinomas but epsilon and frizzled-7, both members of the Wnt/β-catenin signaling pathway showed positivity. Variable cytoplasmic membrane immunopositivity for β-catenin was observed in ACC. In addition, c-myb located at 6q22, was also overexpressed in ACC. Additional genes, which were highly expressed in ACC compared to the other carcinomas, included casein kinase 1.[20]

Genes encoding transmembrane proteins highly expressed in ACC included FAT tumor suppressor which is

Table 2a – Antigens in ACC.

Antigen	Positive	Negative
A new fused gene (MYB-NFIB)[7]	Highly +ve	
C-Kit expression[8]	Highly +ve	
Nerve growth factor[9]	+ve	
Tyrosine kinase A[9]	+ve	
Brain derived neurotrophic factor (BDNF)[10]	+ve	
Heparanase, pRb2/p130, vascular endothelial growth factor, p63, Skp2, EGFR, c-kit, RUNX3[5]	+ve	
Survivin, R1-inducible coiled-coil 1, Geminin[5]	+ve	
Maspin[6]	+ve	
Muscle specific actin, smooth muscle actin or calponin[5]	+ve	
MCM2 (mini-chromosome maintenance proteins)[11]	+ve	
FAT tumor suppressor and transmembrane 4 superfamily membrane1[12]	+ve	
AP-2, macrophage erythroblast attacher[12], versican[13], and laminin-1[12]	+ve	
Sox 4, keratin 17[12]	+ve	
Tumor-associated antigen L6[12]	+ve	
c-myb, located at 6q22[12]	+ve	
Type 4 collagen[13]	+ve	
Casein kinase 1, epsilon and frizzled-7 (members of the Wnt/β-catenin signaling pathway)[8]	+ve	
CK8, CK14 and CK17 and for CK8, CK14, CK17 and CK19[14]	+ve	
Carbohydrate antigen 19-9 (CA19-9)[15]		−ve
E-cadherin and alpha-catenin[15]	Increased as compared to basaloid scc	
Ki-67 labeling index[5]	≥10%	
Hepatocyte growth factor (HGF)[9]	+ve	
CK(AE1/3), CK 34βE12, CK5/6, CK7, CK14, CK18, p63,[5] CA19-9, c-KIT (CD117), PDGFRA, MUC1, and Ki-67[14]	+ve	
CK8,[7] CK20, desmin, S-100 protein, CD34, chromogranin, MUC2, MUC5AC and MUC6[14]		−ve
CAM5.2, CK19, EMA, α-smooth muscle actin, p53, CD10, and synaptophysin[14]	+ve	
CK5/CK7[14]	+ve	
CEA[15]		−ve
Vimentin and S-100 protein[14]	+ve	
Chondroitin sulfate and basement membrane proteins[12]	+ve	
No gene fusion of PLAG1 and mutation of CYLD (Germ-line mutation in cylindromatosis) in ACC tissues[16]	+ve	
CD 43[17]	+ve	

Table 2b – Antigens positive in histological components of ACC like the ductal cells, myoepithelial cells and basement membrane.

Ductal cells +ve in ACC	Myoepithelial cells +ve in ACC	Basement membrane +ve in ACC
	Calpolin[6]	CK5/CK7[14]
	Alpha SMA—weak[5]	Laminin-b1, versican, biglycan, AP-2, macrophage erythroblast attacher and type 4 collagen a-1[13]
S-100[4]	S-100—weak	
Vimentin16	Vimentin	
Amylase, carbonic anhydrase and salivary proline-rich proteins[13]	GFAP9[5]	
	CK14—strong[15]	
	P63—strong[5]	
	CD 10—weak[14]	

downregulated in metastatic prostate cancer. Transmembrane 4 superfamily member 1 also known as tumor-associated antigen L6, encodes a cell surface protein implicated in cell growth. It is highly expressed in several carcinomas including those of the lung, breast, ovary and colon, and has been suggested as a target for monoclonal antibody therapy.[20]

Other genetic changes include loss of chromosomal arms 2q, 5p, 12p and 16q in MEC and allelic loss of chromosomal arm 19q in ACC.[7] Loss of heterozygosity in chromosome 6q23-25 has been found in 76% elcases of ACC.[9]

Overexpressed markers for ACC include laminin-b1, versican, biglycan and type IV collagen-a1. The most underexpressed include amylase, carbonic anhydrase and salivary proline-rich proteins.[7]

Heparanase, pRb2/p130, vascular endothelial growth factor, survivin, R1-inducible coiled-coil 1, geminin, p63, Skp2, EGFR, c-kit and RUNX3 are all histochemical markers for ACC.[4] It showed perineural invasion detected by nerve growth factor, tyrosine kinase[7] and brain derived neurotrophic factor (BDNF).[12]

ACC was consistently positive for cytokeratin (CK) AE1/3, CK 34βE12, CK5/6, CK7, CK14, CK18, p63, CA19-9, c-KIT (CD117), PDGFRA, MUC1, and Ki-67, EMA, CEA, CAM5.2, p53, CD10, S-100 protein and synaptophysin and consistently negative for CK8, CK20, desmin, CD34, chromogranin, MUC2, MUC5AC and MUC6. Vimentin expressed in ACC helps in distinguishing it from PLGA.[14,21]

ACCs displayed well organized basal-luminal differentiation, highlighted by CK5/CK7 immunostaining (Table 2b) (Generally, basally differentiated cells tended to cluster at the inner portion of the tumor sheets, often adopting an "inverted epithelial-myoepithelial pattern"). In contrast, PLGA showed a disorganized histological and immunohistological pattern. C-Kit expression was virtually lacking in PLGA.[13] S-100 showed higher expression in PLGA than in ACC.[9] The level of MCM2 (mini-chromosome maintenance proteins) expression can be used in the differential diagnosis of adenoid cystic carcinoma and PLGA.[10,11]

ACC and mucoepidermoid carcinoma were immunopositive for CK8, CK14, CK17 and CK19 respectively. BSCC (basaloid squamous cell carcinoma) was more frequently associated with decreased E-cadherin and alpha-catenin immunoreactivity than ACC and MEC. Nuclear p53 immunoreactivity was detected more frequently in BSCC than in ACC and MEC. There were no significant differences in p27 immunoreactivity among these carcinomas. Carcinoembryonic antigen (CEA) immunoreactivity was detected in MEC, SCC and adenocarcinoma, but it was not detected in BSCC or ACC. Carbohydrate antigen 19-9 (CA19-9) immunoreactivity was detected only in MEC and adenocarcinoma, but not in BSCC, ACC, or SCC.[14,15]

PLAG1 (pleomorphic adenoma gene 1) and CYLD (cylindromatosis gene) was found not to play a role in ACC tumorigenesis.[8] A high expression of EphA2/ephrinA1 was noted in ACC and hence it was thought to be a novel target for therapy.[11] CD43, a marker of T cells and histiocytes, is preferentially expressed in abluminal cells of ACC and was used to confirm it.[12]

Glial fibrillary acidic protein (GFAP) generally has low sensitivity as a myoepithelial marker. It may, therefore, be useful for distinguishing pleomorphic adenoma from PLGA or ACC.[4,5] The Ki-67 labeling index in ACC (≥10%) is reported to be different from that in basal cell adenoma (<10%).[4]

When the Ki-67 index was less than 5% there were no recurrences, but cases with an index above 10% were often associated with poor outcomes.[8,13]

Hepatocyte growth factor, a protein that causes morphogenesis and dispersion of epithelial cells, indicated invasiveness.[7]

4. Markers of MEC (Table 3)

MEC is one of the most common salivary gland malignancies and is most frequently seen in the 35–65 years age group, and sometimes in children. Microscopically, the MEC is composed of a mixture of mucus producing, epidermoid and intermediate cells. These tumors may be categorized as low grade, intermediate grade or high grade. Distant tumor spread is rare in MEC and occurs commonly many years after diagnosis.[15]

MEC expresses in varying proportions a variety of membrane-bound mucins, including MUC1, MUC4, MUC5AC and MUC5B. High MUC1 expression is associated with high histological grade, high rate of recurrence and metastasis and short disease-free interval. Conversely, expression of MUC4, a surrogate marker of tumor differentiation, is related to low grade, low recurrence rate and a long disease-free interval. Positive staining for MUC5AC is also helpful in distinguishing

Table 3 – Markers for mucoepidermoid carcinoma, acinic cell carcinoma and polymorphous low grade adenocarcinoma.

MEC	Acinic cell carcinoma	Polymorphous low grade adenocarcinoma
MUC1, MUC4, MUC5AC and MUC5B[24]	Maspin –ve[28]	7% of cases EphA2/ephrinA1[22]
Chromosomal translocation: t (11; 19) (q21; p13).[17]	Loss of Y and trisomy 7, 8, and 21[2]	Expression of c-kit: –ve[8]
MECT1–MAML2 fusion[17]	LOH (loss of heterozygosity) on chromosomes 1, 4, 5, 6, and 17[2]	Galectin-3 +ve[26]
CK14 and p63 +ve[5]	DOG1 staining is +ve[5]	
Strong expression of PCNA, p53, and EGFR weak expression of c-erbB2[25]	Carbonic anhydrase VI, and salivary proline-rich proteins[12]	
Strongly positive for TNFa[25]	Keratin, alpha-1-antichymotrypsin, alpha amylase, vasoactive intestinal polypeptide, and myoepithelial markers[27]	
Proteins of the STAT3/PIM1/BCL-2 pathway[25]		
Positive for pAKT[25]		

high grade MEC from squamous cell carcinoma.[16] High CEA levels were found in MEC.

A specific chromosomal translocation has been recognized in mucoepidermoid carcinoma, t (11; 19) (q21; p13), which fuses MECT1 (mucoepidermoid carcinoma translocated-1) at 19p13 with MAML2 (mastermindlike gene family) at 11q21, and the fusion protein is expressed in all different cell types that constitute MEC. This genetic alteration disrupts the Notch signaling pathway.[12] Thus, fusion-positive tumors appear to be much less aggressive than fusion-negative tumors. CK14 and p63 are positive not only in neoplastic myoepithelial cells, but also in basal and epidermoid cell, which is one of the fundamental elements of MEC.[4]

The second most common chromosomal abnormality was single or multiple trisomies, most commonly being +7, +8 and +X. Trisomies were mostly observed in cases not harboring a t (11; 19). Other recurrent abnormalities found were deletions of the terminal part of 6q. Apart from these abnormalities, the t (11; 19) negative MECs showed a heterogeneous pattern of rearrangements with no obvious recurrences.[2]

Patients with an intraoral MEC have a reduced survival expectation if they are male, with regional metastasis, with a high grade malignancy, strong expression of PCNA, p53 and EGFR, or weak expression of c-erbB2. The immunoreactivity of b-catenin showed a significant correlation with histologic differentiation and MEC tumor staging. Despite the rare inflammatory reaction in the parenchymal tissue of the MEC, there was strong positivity for TNFa and DMBT1, which also plays the role of a tumor suppressor in the MEC tumor.[22]

Proteins of the STAT3/PIM1/BCL-2 pathway, which does not belong to p53 mediated signaling showed positivity and BCL-2 which was strongly positive both in intermediate and clear tumor cells, was thought to play an important role in the antiapoptotic survival of tumor cells.[22]

MEC was markedly positive for pAKT, involved in cell survival reactions to various metabolic stresses.[22]

5. PLGA markers (Table 3)

PLGA is a rare, asymptomatic, slow-growing malignant salivary gland tumor most commonly found in the palate. It shows polymorphism histologically and can be confused with ACC and PA. It is non-aggressive when compared to other oral cavity tumors. Expression of c-kit, a transmembrane receptor tyrosine kinase, has recently been reported to be not expressed in PLGA. Also expression of galectin-3, a non-integrin beta-galactosidase-binding lectin, has been reported to be significant in PLGA and decreased in ACC.[17]

6. Markers for acinic cell carcinoma (Table 3)

Acinic cell carcinoma is a tumor most commonly found in the parotid gland. The disease presents as a slow-growing mass, sometimes associated with pain or tenderness and they resemble serous acinar cells. They may show few mitotic figures and shows a multidirectional differentiation towards acinar, ductal as well as myoepithelial elements. Variable growth patterns such as solid, microcystic, papillary cystic and follicular are seen. It may have prominent lymphoid follicles at periphery and psammoma bodies. Basophillia and prominent lymphoid infiltrate should arouse suspicion of acinic cell carcinoma.

It is necessary to identify serous acinar differentiation for the diagnosis of acinic cell carcinoma. However, a positive signal for α-amylase, a specific marker of normal acinar cells, is not detected in many acinic cell carcinoma cases, so it is not always useful for the diagnosis. It has recently reported that DOG1 staining is a marker of salivary acinar cells, and strong staining can be used to diagnose acinic cell carcinoma.[4]

Amylase, carbonic anhydrase VI, and salivary proline-rich proteins are found in neoplasms having acinar differentiation such as acinic cell carcinoma.[20] Keratin, alpha-1-antichymotrypsin, alpha amylase, vasoactive intestinal polypeptide and myoepithelial markers are also positive and the granules are PAS + diastase resistant. The tumor may have focal neuroendocrine staining.[23]

Acinic cell carcinomas showed LOH (loss of heterozygosity) in chromosomal arms 4p, 5q, 6p and 17p, which were frequently altered.[2]

Acinic cell carcinomas did not show any maspin expression.[24]

7. Carcinoma ex-pleomorphic adenoma (PA)

The genes MDM2 (Mouse double minute 2 homolog) were co-amplified in carcinoma ex PA. There are high HMGA2 expression levels. Cerb-B2 expression has been detected and can help

distinguish it from atypical PA. Mutation and over-expression of TP53 are also seen.[2] Alterations of chromosome 8q21 and 12q13-15 is frequent in carcinoma ex-pleomorphic adenoma, similar to its benign counterpart. Loss of heterozygosity is seen at 12q loci in chromosome 12q13-15.[12]

8. Random tumor markers in SGTs

The E-cadherin, which has been implicated in cancer progression and metastasis of epithelial cells, including the salivary gland, is lost in more undifferentiated and invasive epithelial SGTs.

Markers detecting metastasis include B72.3, which showed the strongest staining in the low grade carcinomas and reactive with a high molecular weight glycoprotein complex termed TAG (tumor-associated glycoprotein)-72. It is a marker detected especially in adenocarcinomas. These results suggest that B72.3 may be a useful marker for glandular differentiation in the fine needle aspirates of mucoepidermoid carcinomas.[25] c-erbB-2 immunostaining was a prognostic marker of poor clinical outcome, regardless of tumor site, size or grade and lymph node status.[26]

SGT are heterogeneous in terms of tumor types, and it varied from patient to patient. Hence in one patient, ACC was c-Kit positive, making it a possible target for Imatinib, whereas in another patient, it was negative.[18] KIT proteins are important during embryogenesis, including gametogenesis and hematopoiesis and hence has been demonstrated in hematopoietic neoplasms, melanomas, gynecological tumors, thyroid, lung cancers, seminomas and gastrointestinal tumor. In salivary gland neoplasms, only a few reports have shown alterations in KIT and that too in the ACC.[27]

It is believed that the elevated expression of HIF-2α, TWIST2 and SIP1 can contribute to invasion and metastasis of ACC.[28] Hepatocyte growth factor (HGF), a protein that causes morphogenesis and dispersion of epithelial cells, has been found to increase ACC scattering and perhaps invasiveness.[9]

Newer research in SGT is focusing on factors that increase tumor invasion and spread. Matrix metalloproteinase-1, tenascin-C and beta-6 integrin have been found to be associated with benign tumor expansion and tissue invasion by malignant tumors.[7]

Rare and newly identified types of adenocarcinomas need to be understood and they include:

Sclerosing polycystic adenosis (SPA) was first characterized in 1996 as a rare lesion of uncertain nature with a striking morphological resemblance to fibrocystic changes of the breast. Frequently misdiagnosed as acinic cell carcinoma, it occurs in patients 33–44. 5 years with a female:male ratio of 3:2. Most cases arise in the major salivary glands, but rare cases can involve intraoral minor salivary glands. The patients present with a slow-growing well circumscribed and partially encapsulated mass. Histologically, there is proliferation of microcysts, ducts and acinar structures which can be widely spaced or crowded, in a sclerotic stroma, and with focal lymphocytic infiltration.

Immunohistochemically luminal epithelial cells express EMA, BRST-2, estrogen receptor (focal) and progesterone receptor (focal), but not c-erbB2.

An uncommon signet ring cell adenocarcinoma of the minor salivary gland has recently been characterized and this behaves as a low grade malignancy. The mean age of patients is 56.4 years with a female predilection. The tumor is infiltrative and comprises narrow parallel strands, randomly scattered small nests or isolated cells. Signet ring cells predominate and possess single or several cytoplasmic mucin vacuoles and eccentric indented nuclei. Mitotic figures are rare or absent. Perineural invasion is not uncommon.

9. Salivary duct carcinoma

Salivary duct carcinoma (SDC) is thought to be a distinct malignancy of the major salivary glands because of its highly aggressive behavior and resemblance to ductal carcinoma of the breast. The tumor occurs in elderly men, predominantly in the parotid gland. Histologically, it shows a striking resemblance to breast carcinoma of the ductal type, presenting intraductal and invasive components. SDC is considered to have one of the worst short-term prognoses. The markers that have been studied include Ki-67, proliferating cell nuclear antigen, c-erbB-2 and p53.[12] Protein-15 and androgen receptor (AR) are frequently positive in this tumor. The estrogen receptor and progesterone receptor are not detected in most SDC and they help to differentiate the metastasis from the breast. Prostate-specific antigen is occasionally detected in this tumor. Variants of SDC include invasive micro papillary variant, sarcomatoid variant, intraductal carcinoma.[12]

10. Small cell carcinoma

Small cell carcinoma of the major salivary glands is an aggressive malignancy, with more than half of patients developing local recurrence or distant metastasis comparable to that of cutaneous Merkel cell carcinoma and small cell carcinomas express CK20, similar to Merkel cell carcinoma.[12]

It has been seen that suppression of Id1 plays a role in SGT, and could represent an effective approach for the treatment of salivary gland cancer.[29]

The PI3K/AKT/mTOR signaling axis controls cell proliferation and survival and has achieved major importance as a target for cancer therapy.[30]

The Ki-67 proliferative index is the most widely used immunohistochemical marker for prognosis of salivary gland carcinomas. A high Ki-67 index has been found to correlate with poor overall survival in MEC, acinic cell carcinomaa and ACC.[18]

Heparanase expression is increased in SGTs and is a valid target for the anticancer drugs.[31]

NM23 (Nucleoside-diphosphate kinase A) protein is a nucleoside-diphosphate kinase that plays a tissue-specific role in relation to tumor metastasis. Cytoplasmic NM23 staining can be demonstrated in majority of PA, ACC and MEC, with no significant difference in the frequency of positive cells among these tumors. However, nuclear expression of NM23 is restricted to malignant salivary gland tumors with metastasis. Hence, nuclear NM23 staining may be used for predicting metastasis in SGCs.[32]

The number of separate tumor entities to be considered in differential diagnosis has greatly increased in the latest two WHO classification systems. The experience is that the clinical behavior of some salivary gland carcinomas does not correlate well with their histopathologic classification and that tumors classified within the same category may exhibit quite different clinical outcomes.

11. Conclusion

With our expanding understanding of the pathogenesis and molecular alterations in different tumor types, new targets will continue to be proposed for diagnosis, prognosis and therapeutic applications. The pathologist needs to be familiar with the molecular alterations so that there may be a strong potential to implement good treatment.

The clinical stage is of higher prognostic value than histology and grade of malignancy. High proliferative activity (Ki-67 > 30%) is the strongest negative predictor in salivary gland cancer. Despite several developments, SGCs still remain a heterogeneous group of tumors challenging both pathologists and clinicians alike.

Conflicts of interest

The author has none to declare.

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